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INCREASE INCIDENCE OF KAWASAKI DISEASE SOMETIMES WITH BCG SCAR REACTIVATION DURING CORONA PANDEMIC

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ABSTRACT

Kawasaki disease is an acute vasculitis of childhood. The disease was described in Japan in 1967 by Dr. Tomasaku Kawasaki(1).

The etiology of KD remains unknown despite extensive research. Many of the clinical features resemble with childhood exanthematous infection with fever lead to the investigation of many infectious agent as etiological factor of Kawasaki Disease. It is observed that the ongoing Covid 19 Pandemic is associated with an increase incidence of Kawasaki Disease. At the end of April 2020 and the begining of may 2020 we identified a higher number of Kawasaki disease cases, some of them with BCGitis that was related to Covid 19 Epidemic in West Bengal ,starting 4 to 6 week of the disease. Similar observation was also reported from different part the World including India. Interpretation of my observation suggest that Human Corona Virus would be related to KD/IKD and that may thrown light to the treatment of Covid 19 disease at least in Pediatric population.

Aim of Study: The aim of this study is along with increase incidence of KD/IKD with BCG Scar reactivation ,What are the relation of pathophysiological process and treatment of both the condition. I retrospectively considered the patient attended at my OPD since July 2019 to July 2020. The Patient diagnosed as KD/IKD before the epidemic and during this period are compared. It is found that the incidence of KD/IKD increase during Covid 19 Pandemic situation. The child who were diagnosed as the KD/IKD, referred to Pediatric Hospital for better management.

KEY WORDS: KD (Kawasaki Disease), IKD (Incomplete Kawasaki Disease), BCG Scar, COVID 19, IVIG, Aspirin.

Pathophysiology of KD/IKD:
The incidence of KD in United States and Japan are 25 per one lakh and 250 per one lakh children under 5 years of age respectively. After 7-9 days of the onset of fever there are proliferation of CD8+ (Cytotoxic) lymphocytes and immunoglobulin A producing plasma cell. The inflammatory cells Secretes various Cytotoxic factors(eg-Tumor Necrotic Factor, Vascular endothelial growth factor etc), monocyte chemotactic and activating factor, interleukin(eg-IL1, IL4, IL6 etc) and matrix metalloproteinase (MMP3 and MMP9) that target the endothelial cells. It is a systemic inflammatory process that affect 6 months to 5 years of age children. It can involve multiple organ and tissue like Cardiovascular, Respiratory, GIT, Lymphoreticular system etc. The pattern of immune response with B-lymphocyte and CD8 T-Lymphocyte is consistent with an adaptive immune response to an intracellular pathogen such as virus. The studies revealed the presence of a specific antigen in acute Kawasaki disease bronchial epithelium and in macrophages within inflammed Kawasaki disease tissue(2)

Pathophysiology of Covid 19:
SARS Cov2 is a single stranded enveloped RNA virus of 30 kb. It has spike protein "S". The spike protein is the major determinant of cell tropism and hence interspecies transmission of Cov's since it binds the virus to a cellular receptor and subsequently catalyzes virus entry by membrane fusion. The S1 domain further divided into an "N" terminal domain (NTD) and "C" terminal domain (CTD). The NTD exhibits a sugar at the cell surface and serves as an attachment factor. The CTD is responsible for the binding to the host receptor angiotensin converting enzymes (ACE). Human corona virus genera alpha such as 229 E and NL63 are responsible for common cold and croup. NL 63 is also related to KD. Middle east respiratory Syndrome corona virus (MERS- CoV) and SARS CoV2 are classified to Beta corona virus. The patient with severe disease have increased plasma concentration of the following cytokines including interleukin 6 (IL6),Interleukin 10(IL10), granulocytes colony stimulating factor (G- CSF) and tumor necrosis factor alpha(TNF) etc.(3) It is found that CRP was significantly associated with the progression of covid 19 disease . CRP levels also is positively co related with lung lesion and reflects disease severity.(4) The research evidence suggests that there is blood clotting abnormalities with covid 19 disease.(5)

BCGitis:
BCG Scar reactivation (fig1)is seen up to 50% cases of Kawasaki disease. It is unique early specific sign of KD/IKD not included in diagnostic criteria.(6) BCGitis rarely may be seen with measles.(7)

Fig-1: (BCG Scar Reactivation with 1 year old Boy with Kawasaki Disease)

Shared Pathophysiological features of COVID 19 and KD.

COVID 19	KD
1. Etiology-RNA virus, SARS CoV 2	1. Etiology-Not known. Many infectious agent Implicated like Corona virus NL63,HCoV- NH
2. Organ involved : Lung followed by other	2. Lung, CVS,GI etc.
3. Marker of inflammation IL – 6, IL -10, GCSF, TNF	3. IL6,IL4,IL10, TNF
4. Predominant Cell CD4+ and CD8+, T cell Play critical role.	4. CD8+ T lymphocyte predominate over CD4
5. Prolong fever	5. Prolong fever.
6. CRP associated with progression of disease.	6. CRP associated with KD. IV IG resistant patient showed a sustain high value of CRP
7. Self limiting disease.	7. Self limiting disease.

Association between a novel human corona virus and KD:
Recently cluster of children are reported with KD/IKD like disease throughout the World including India. Some are positive for SARS COV 2. Many Infectious etiological agents are under investigation, human corona virus NL63 one of them.(9,10).Kawasaki disease is a systemic vasculitis of unknown origin. There is evidence of a novel human corona virus known as "New Heaven Corona Virus"(HCoV NH) associated with respiratory secretion of infant with Kawasaki disease. These case control studies shows that HCoV NH infection has an association with KD.(11)

Role of IVIG and aspirin in KD and Covid 19:
IVIG was first used in 1952. It is pulled immunoglobulin G(IgG), prepared from more than thousand blood donors. It consist of more than 95% unmodified IgG and trace amount of IgA & IgM. In Kawasaki disease 2 gm/Kg over 10-12 hrs intravenous immunoglobulin highly effective. It reduces Cytokine and Chemokine level, changes in cell population like decrease CD-14+ Monocyte/macrophages, neutrophils activated T-Cells, increase number of circulating NK cells. Regulation of T cell at the tissue level for the resolution of inflammation in KD is important.(12,13)

Aspirin is useful to reduce fever, inflammation in KD. It is an Anti platelet at low doses and prevent blood clot formation in coronary artery aneurysm in KD (14). The treatment aim of KD is to reduced inflammation and prevent cardiac complication. The American Heart Association guidelines recommend for intravenous immunoglobulin (2 gm/kg over 12 hours) in combination with high dose aspirin (80-100mg/kg per day divided into four doses). If coronary artery disease developed and persist low dose aspirin may be required for live long. IVIG modulates cytokine production and alter T cell activity, Where as aspirin reduces inflammation and decrease the risk of thrombosis.(14,15) Aspirin in covid 19 inhibits viral replication. It also has anti platelet, anti inflammatory and anti lung injury effect. IVIG clearly effective in the treatment of covid 19 but with side effect. Aspirin shortens Hospital stay and reduces CVS complication.

CONCLUSION:
It is observed that a high number of KD/IKD cases following the SARS CoV-2 epidemic with at least 3 times higher incidence among my patients attending OPD for consultation. Retrospectively all the patient attended the OPD for consultation during July 2019 to July 2020 were considered. Between march 2020 to june 2020 two patient were presented at my OPD with fever, Skin Rash and BCG Scar reactivation. They were diagnosed as IKD and referred to Pediatric Hospital for better management .In Kawasaki Disease the blood vessels swell and become inflamed. The symptoms often resolved spontaneously without medical evaluation and treatment however serious complication may develop. Patient have hyper inflammatory response. The protein involve in that inflammation starts circulation in the body at high level, blood clots organ throughout the body. The pathophysiological process, etiology etc shares both covid 19 and Kawasaki disease. IVIG with Aspirin highly effective in the treatment of KD, also may be considered in Covid-19 disease. No absolute factors ,comorbidities are there to explain the morbidity and mortality of COVID 19 disease .There may have a single gene which may take sole responsibility for this explanation. The entry and exit point of corona virus is head neck region, more specifically nose and mouth. We need to secure that area with effective barrier till the vaccine and specific treatment available.

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